TABLE 4.—*Some of the Side-Effects, Real or Purported, Ascribed to Estrogen-containing Contraceptive Agents*

Minor
Weight gain and edema
Nausea, vomiting and change in bowel habits
Vaginal spotting
Migraine headaches
Increased serum globulins-confusion in hormone measurement
Chloasma
Hirsutism
More Serious
Hypertension
Thrombophlebitis and embolic disease
Intrinsic vascular changes
Cerebral vascular occlusive disease
Impaired carbohydrate tolerance
Unknown risk of cervical neoplasia
Liver disease
Hyperlipidemia
Post treatment amenorrhea and galactorrhea

the premature presence of the ovum in an unprepared uterus.[19] This form of contraception has little attractiveness for use in women with frequent coital exposure. It does have great potential, however, for the women with infrequent or unpredicted exposure, including cases of criminal rape.

One progestogen, norethindrone, in large doses was found to provide low protection as a postcoital contraceptive.[20]

Complications of Contraceptives

Whenever drugs are administered to healthy persons for experimental or prophylactic purposes, great concern is appropriately expressed about possible side-effects. When such drugs are administered to millions of people, even a low incidence of serious side-effects may become an important health problem; such is the case with the estrogen-containing contraceptives. These agents, initially demonstrated in animal or human trials to be remarkably safe, now, after almost two decades of use by patients, have been demonstrated to have many minor and a few, although unusual, serious side-effects.[21] Many of these real or purported side-effects are listed in Table 4.

The minor complications of vaginal spotting, edema, nausea, and chloasma are not uncommon. Migraine headaches can be a troubling problem in predisposed women. The migraine seems to be precipitated by the falling levels of steroids which occurs at the time of monthly discontinuation of therapy.

Estrogens have many metabolic effects on the liver. These effects will be discussed in detail later by Dr. Fisher.

Also seen in Table 4 are the more serious side-effects. An analysis of the role of contraceptive agents in the production of these complications will be presented in the following sections.

An Analysis of the Reported Association of Oral Contraceptives to Thromboembolic Disease

WILLIAM D. ODELL, MD, PhD*

DR. SWERDLOFF has reviewed the mechanism of action and various types of oral contraceptives in present use. Oral contraceptives have become one of the commonest forms of contraceptive devices and millions of women throughout the world have been taking them for several months to many years. While the incidence of serious side-effects attributed to these drugs is low, some of them are life-threatening. If these side-effects are causally related to oral contraceptive treatment, then the total number of people affected will be very large. Thus, understanding the cause-and-effect relationship of side-effects should be thorough. At the outset it should be said that the possible statistical increase in life-threatening side-effects in women without predisposing factors is very low. We will attempt to put that in perspective later in this review.

Thromboembolic Disease

The initial studies in the United States reported that women receiving oral contraceptives were no more likely to have thrombophlebitis or embolic phenomena than were those not receiving oral contraceptives. For example, in 1963 the Food and Drug Administration of the United States reviewed more than 350 reports of thromboembolic diseases in women taking Enovid® (norethynodrel with mestranol).[22] They estimated that among white women taking Enovid the mortality from thromboembolic disease was 12.1 per million, whereas the comparable mortality in the general

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TABLE 5.—*Use of oral contraceptives by women who died of pulmonary embolism. Numbers expected from experience of control women of similar age and parity are shown in parentheses.†*

Predisposing Conditions	*Number of Deaths Among*		
	Users of Oral Contraceptives	*Nonusers of Oral Contraceptives*	*All Women*
Absent (class A)	16 (4.2)	10(21.8)	26
Present (class B)	9 (6.8)	40(42.2)	49*
Total (class A and B) ...	25(11.0)	50(64.0)	75

*Two patients whose contraceptive practice was unknown omitted from this category.

†Reprinted by permission from Inman and Vessey: Br Med J 2:193, 1968.

TABLE 6.—*Use of oral contraceptives by women who died of cerebral thrombosis. Numbers expected from experience of control women shown in parentheses.†*

Predisposing Conditions	*Number of Deaths Among*		
	Users of Oral Contraceptives	*Nonusers of Oral Contraceptives*	*All Women*
Absent (class A)	5(1.5)	5 (8.5)	10
Present (class B)	0(1.5)	16(14.5)	16*
Total (class A and B) .	5(3.0)	21(23.0)	26

*One patient omitted from this category whose parity was unknown (nonuser).

†Reprinted by permission from Inman and Vessey: Br Med J 2:193, 1968.

TABLE 7.—*Affected and control patients classified by use of oral contraceptives during month before onset of disease episode (or during month before hospital admission in case of patients undergoing elective operation). (Percentages shown in parentheses)**

Diagnostic Group	*Number of Patients*		
	Users of Oral Contraceptives	*Nonusers of Oral Contraceptives*	*All Women*
Thromboembolism	26(45)	32(55)	58(100)
Control	10 (9)	106(91)	116(100)
Both groups	36(21)	138(79)	174(100)

*Reprinted by permission from Vessey and Doll: Br Med J 2: 199, 1968.

population was 8.4 per million. They concluded that there was no significant increase in the risk of death from thromboembolic disease in women receiving Enovid but advised that further studies be performed. Further consideration revealed that healthy young women probably should have a lower incidence of thromboembolism than the entire population, which includes older age groups and persons with other predisposing factors. In 1966 the Food and Drug Administration stated that 5,000,000 women were taking oral contraceptives and that 85 deaths would have been expected from thromboembolic phenomena based upon the national mortality statistics.[23] However, only 13 deaths were reported in these women receiving oral contraceptives. Surprisingly, the same year the Committee on Safety of Drugs received reports of 19 deaths per 400,000 women receiving oral contraceptives and 10 of these 19 had no predisposing factors.[24]

In 1968 Inman and Vessey,[24] and Vessey and Doll[25] first reported studies which appeared to indicate that thromboembolic phenomena *might* be increased in women receiving oral contraceptives. Inman and Vessey[24] reviewed 309 deaths* reported to be caused by thromboembolic phenomena in the British Isles (Table 5). Seventy-seven of these patients had pulmonary thrombosis or embolus, 205 had coronary thrombosis or myocardial infarction and 27 had cerebral thrombosis or embolus. It is important to understand the investigators' method of control selection. They asked each physician who cared for one of the patients to go to the place in his records where that patient's chart would have been kept, and to move backwards or forwards from that position, selecting two, and later three or four women in the same age range. These patients were then located and interviewed for predisposing factors and oral contraceptive use. In this manner, 998 suitable controls were gathered and the percent of these control subjects taking oral contraceptives was obtained and related to the age of the patient and her parity. Note from Table 5 that the number of women receiving contraceptives in the group who had pulmonary embolism was greater[46] than that expected from the control groups.[32] In a similar manner, they studied the incidence of cerebral thrombosis and embolism (Table 6), and concluded that the incidence of these diseases is probably increased in women receiving oral contraceptives. The incidence of coronary thrombosis was not significantly greater and no firm conclusion was made. In a separate article, Vessey and Doll[25] in 1968 reviewed the data from 19 general hospitals, each of which had more than 300 beds, and identified patients admitted with deep vein thrombosis or pulmonary embolus. (It is to be noted that the first article[24] dealt with deaths, the second[25] with hospital admissions.) For each pa-

*344 deaths were reviewed, but 35 patients were eliminated from study for various reasons, such as the fact that they were postpartum.

TABLE 8.—*Relative Risks of Thromboembolism at Various Dose-Levels of Estrogen (Data for United Kingdom)**

	Mestranol Estrogen Dose (μg)				*Ethinyloestradiol Estrogen Dose (μg)*		*Number of Reports*
	150	100	75-80	50	100	50	
Fatal pulmonary embolism	6.0	3.3	2.1	1.2	2.2	1.0	59
Non-fatal pulmonary embolism	3.2	1.7	1.3	1.4	2.5	1.0	234
Deep venous thrombosis of lower limb	1.9	1.4	1.1	1.2	3.3	1.0	235
Other venous thrombosis of lower limb	1.9	1.3	1.3	2.1	1.8	1.0	252
All venous thrombosis	2.4	1.6	1.2	1.5	2.5	1.0	780
Cerebral thrombosis	3.9	1.4	0.8	0.6	..	1.0	79
Coronary thrombosis	3.0	1.4	0.3	1.3	2.1	1.0	61

*Reprinted by permission from Inman et al: Br Med J 2:203, 1970.

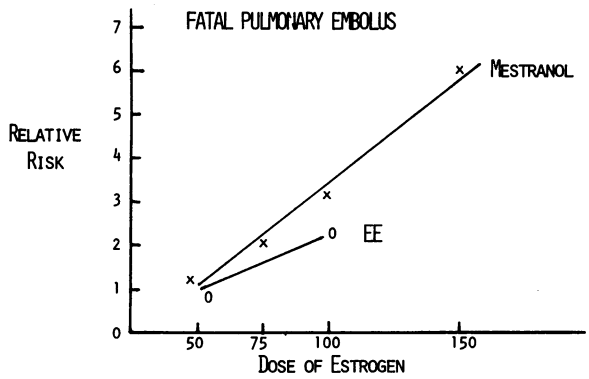

Chart 8.—Graph of the relative risk of fatal pulmonary embolus plotted against dose of estrogen in the oral contraceptive used. (Plotted from Inman WHW et al: Br Med J 2:203, 1970)

tient identified they obtained two control patients from the same hospital and selected those controls as patients admitted at the same time but having acute medical or surgical conditions, other than thromboembolic phenomena or admitted for elective operation. They found that 45 percent of the patients having thromboembolic disease were taking oral contraceptives but only 9 percent of the control patients were taking oral contraceptives (Table 7). There was again no significant difference in the patients who had coronary thrombosis or infarction. The investigators concluded (from this study design) that "risk of hospital admission for venous thromboembolism is about nine times greater in women taking oral contraceptives than in those who do not." Vessey and Doll[25] extrapolated these findings to the national population, calculating that 1 in every 2,000 women using oral contraceptives are admitted with idiopathic venous thromboembolism in comparison with about 1 in every 20,000 women not using them.

Most recently, Inman, Vessey, Westerholm and Engelund[26] attempted to relate the incidence of thromboembolic disease to the steroidal content of oral contraceptives. This study published in the *British Medical Journal* in 1970, took reports of all patients who had thromboembolic disease and used oral contraceptives that had been received by the Drug Safety Committee in the United Kingdom and in Sweden and Denmark. These reports were analyzed for the type of oral contraceptive used, and correlations were calculated between the doses of estrogen and the risk of pulmonary embolus, deep vein thrombosis, cerebral thrombosis and coronary thrombosis or infarction. These data, shown in Table 8, indicate there is a strong correlation between the estrogen content and the incidence of the above disease states within patients in the United Kingdom. In Sweden and Denmark, there was a similar association in venous thrombosis and pulmonary embolism and estrogen content, but no relation to cerebral thrombosis could be found. When the sequential versus combined contraceptives were studied separately, no differences were observed; the relationship held only for estrogen content. In addition, no differences were noted when the two common estrogens, ethinyl estradiol and mestranol, were compared. Chart 8 shows diagrammatically the relationship between estrogen dose and fatal pulmonary embolism, the most dramatic example of the data collected. It is to be noted that these investigators obtained the expected incidence of thromboembolic phenomena by reviewing the percent of market sales attributable to a particular brand of contraceptive. They then multiplied this percent by the total number of patients having the adverse reaction studied (all of whom took oral contraceptives by selection). They gave this example: Ovulen® (ethynodiol diacetate) accounted for 22.23 percent of the total market sales; there were 75 reports of nonfatal pulmonary embolism—75×22.23 per $100 = 16.67$, which is the number of patients with pulmonary embolism and taking oral contracep-

TABLE 9.—*Comparative Incidence of Superficial and Deep-Vein Thromboembolic Disease in Women of Childbearing Age†*

Based on	*Cases per 1,000 Woman Years*
Normal incidence	
Hospital admissions	0.91 (0.84 - 1.08)
Visits to physicians	2.20 (1.20 - 3.00)
Antenatal incidence	0.61±0.19*
Oral contraceptive studies	0.97±0.62

*Nine month rate extrapolated to 12 months for comparison with other annual rates.

†Reprinted by permission from Drill V: JAMA 219:583, 1972.

tives that would have been expected to have been taking Ovulen. The incidences thus calculated were compared to the actual incidence data.

Similar findings have been reported now in two studies in the United States.[27,28] For example, Sartwell et al[27] performed a retrospective study published in 1969. They identified 175 women, aged 15 to 44, discharged alive from 43 hospitals after an initial attack of idiopathic thrombophlebitis, pulmonary embolism or cerebral thrombosis or embolism. One hundred and seventy-five hospital controls were matched casewise with each case at the hospital according to: residence, time of admittance to hospital, race, age, marital status, parity and pay status. Both groups of patients were free of chronic conditions either associated with thromboembolism or constituting contraindications to pregnancy. Forty percent of the patients who had thromboembolism and 13 percent of the control patients had received oral contraceptives within one month before the time of admittance to hospital. From this study, the relative risk of thromboembolism for the oral contraceptive users was estimated to be 4.4 times that of the non-users. These investigators found the risk was higher with the sequential contraceptives than with combined contraceptives. However, the estrogen content of the two medications was not given nor discussed.

In 1971, Böttiger and Westerholm[29] in Sweden analyzed 400 cases of thromboembolic disease in women receiving oral contraceptives, reported to the Swedish Adverse Drug Reaction Committee. From knowledge of the population use of oral contraceptives in Sweden, they estimated that the risk of having thromboembolic manifestations was 1 in 3,600 users of oral contraceptives, as compared with 1 in 23,000 non-users of oral contraceptives, or 1 in 340 during normal pregnancy. The mortality risks were estimated at 0.9 patients per 100,000 users per year. The patients studied by Böttiger and Westerholm included patients with deep vein thrombosis, cerebral thrombosis, myocardial infarction, both those who survived and those who died of their disease.

In contrast to these series of publications (utilizing selected controls and retrospective studies) which suggest increased incidence of thromboembolic disease with oral contraceptives, three papers have appeared in the *Journal of the American Medical Association,* written by Drill and Calhoun,[30-32] which review the total world literature on this subject and conclude that there is not an increased incidence of thromboembolic phenomena in patients receiving oral contraceptives. The overall incidence of thrombophlebitis in nonpregnant women of childbearing age was obtained from a series of publications which obtained data between 1957 and 1966. Based upon these publications, the incidence of hospital admissions for superficial and deep vein thromboembolic episodes was estimated to average 0.9 cases per 1,000 women per year. If patients who visited the physician in his office were included, the rate increased to an average of 2.2 cases per 1,000 per year. Drill made independent calculations from the Royal College of General Practitioners Study[33] which indicate a rate of about 1.3 cases per 1,000 women per year. Expecting this control statistic, Drill reviewed the incidence of superficial and deep vein thromboembolic disease in all published large-scale studies with oral contraceptives. These data are reviewed in Table 9 and indicate that an average of 0.91 cases per 1,000 women per year was observed. This is not increased over the control population, but is significantly higher than the antenatal group (which is also exposed to estrogen and progestogen). Drill also reviewed all the reported small-scale prospective studies with oral contraceptives and obtained an overall rate of thromboembolism (fatal and nonfatal) from some 53 publications of 1.22 per 1,000 women per year, also not significantly different from controls. Drill went further and took data from Vessey and Doll[25] concerning the incidence of recurrence in women continuing oral contraceptives after having had one thromboembolic episode. Two series of patients were reviewed, one composed of 21 patients and a second of 29 (the 21 original plus eight more) with a history of thrombophlebitis, some of whom had continued taking oral contraceptives. Table 10 presents Drill's summary of Vessey and Doll's data, which revealed no significant differ-

TABLE 10.—*Recurrence of Thromboembolism in Treated and Untreated Women**

	Number Cases	Disease Recurrence: Not Using Oral Contraceptives	Disease Recurrence: Using Oral Contraceptives
1968	21	12 (57%)	9 (43%)
1969	29	17 (59%)	12 (41%)

*Reprinted by permission from Drill V: JAMA 219:583, 1972.

ence between patients who were taking oral contraceptives and those who were not. Drill went on to divide the published studies into prospective studies in which the drug is administered to groups of women and the occurrence of cases of thromboembolic diseases recorded; and retrospective studies, which are analyses of hospital records with selected control groups. He reviewed the 15 large prospective studies and the 53 small-scale prospective studies, and came to the conclusion previously given: "There is no increase in thromboembolic phenomena in women taking oral contraceptives." It is to be noted, however, that these prospective studies did not include selected control groups matched for age, parity, and other such factors, but took the incidence of thromboembolism in the population as a whole as its control. The retrospective studies that we reviewed above are the ones that have indicated increased thromboembolic phenomena. Their controls were selected in the fashion described, although Drill quotes a statistical text of Mainland *(Elementary Medical Statistics)* to correctly point out that retrospective studies cannot be used to prove cause and effect relationship; they can be used to suggest an hypothesis of cause and effect. Prospective studies should be used to prove the relationship. Drill, however, neglects to add that even prospective studies must be designed correctly to include control groups handled in the same fashion as treated groups. The latter has not been true for the prospective studies reviewed by Drill (or existing in the literature for our review). Thus the proof that no cause and effect relationship exists between estrogen containing oral contraceptives and thromboembolic phenomena is on as shaky grounds as is the statement that there is such a relationship.

Goldzieher[34] has critically analyzed some of the publications on thromboembolic hazards that appeared in 1970. He indicates that the incidence of any idiopathic thromboembolic disease has increased strikingly in some countries independent of the introduction of oral contraceptives—in

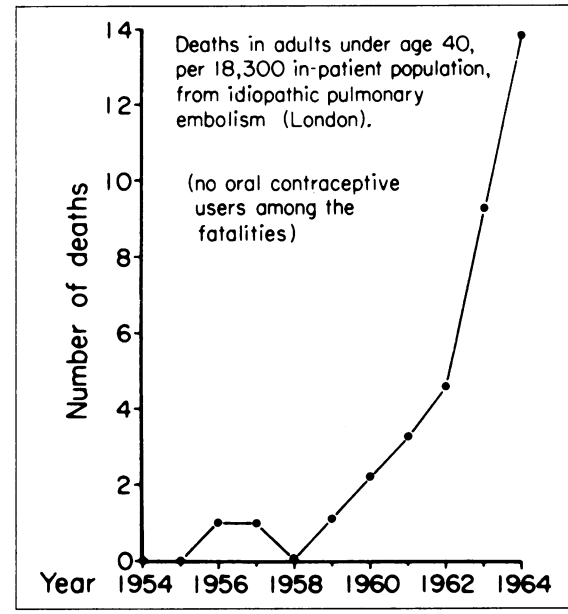

Chart 9.—The change in number of deaths from idiopathic pulmonary embolism in London during the years 1954 to 1964. (Reproduced by permission from Goldzieher JW: Contraception 1:409, 1970)

other words, in patients not receiving oral contraceptives. This incidence is shown on a graph from his publication in Chart 9. This increase of thromboembolic disease may be related to decreased ambulation that has come with increased use of the automobile and other transportation devices, for thromboembolic phenomenon remains very low in certain countries of the world where ambulations remain high. The increase occurs in both sexes and, as indicated in Chart 9, in women who never used oral contraceptives. Goldzieher also points out (as Drill did) the antenatal incidence of thromboembolic disease is not increased over the normal population. Goldzieher summarized data that he collected in a single, closely coordinated, computerized clinical trial of 23,217 women observed monthly for a total of 363,469 cycles. The dropout rate was unusually low in this cycle and the incidence of thrombophlebitis in women examined every month turned out to be surprisingly low—0.56 per 1,000 women per year, very close to the figure previously stated from the general population review of world literature by Drill and Calhoun. Goldzieher criticizes the retrospective studies, previously described, of the College of General Practitioners, stating that the number of thromboembolic patients was small and that patients with predisposing conditions other than pregnancy or postpartum state were not excluded

or commented on. He comments that the possibility of thrombophelebitis being associated with oral contraceptives is masked by the inclusion of such patients. However, a difference was observed even in these diluted sample studies, and Goldzieher states that one must conclude that either the contraceptive-caused thromboembolism is very common (an inference negated by subsequent British studies) or that the comparison is severely biased. The same group of British investigators, Goldzieher points out, have reported an association of meclozine with fetal abnormalities, a finding subsequently shown to be incorrect.

Finally, Goldzieher assembled the mortality risk for women due to pregnancy and various forms of contraceptives. Since the risk of pregnancy per se is greater with other contraceptive devices and lowest with oral contraceptives, the mortality risk from the sum of pregnancy and other contraceptive devices is greater than the sum for oral contraceptives. These data are presented in Table 11.

Certain other studies involving treatment with estrogens, men for atherosclerotic heart disease or prostatic cancer and women for lactation, also bear on our discussion. Daniel el al[35] reported that there was a tenfold increase in thromboembolism in women postpartum receiving 30 to 60 mg of stilbestrol daily as compared with lactating women not receiving the stilbestrol. All eight cases of pulmonary embolism observed occurred in the treated group. In 1963, Stamler et al[36] reported a well controlled study of estrogen therapy for myocardial infarction in middle-aged men. High doses (10 mg conjugated equine estrogens per day) were given to one group of men for three months after a myocardial infarction. The treatment group had a 21.7 percent recurrence; the placebo group had a 4.6 percent recurrence. Two well controlled studies of estrogen treatment of prostatic cancer in men were performed by the cooperative Veterans Administration Hospital group in the United States[37,38a] and one by Bailar reported in *Lancet.*[38b] In the study by Bailar, 5 mg of stilbestrol was given daily and the patients compared with a control group not receiving estrogen. There were increases in deaths due to heart disease and cerebrovascular accidents in the group receiving this high dose of stilbestrol. These data are summarized in Table 12. In the well controlled Veterans Administration Hospital studies, there was also a striking increase in deaths in the men receiving 10 to 15 mg of stilbestrol daily.[37] The study was discontinued when the differences became statistically significant. Later a well controlled study using 5 mg of stilbestrol was carried out.[38a] In this study, in contrast to the report of Bailar[38b] in men post-infarction, 5 mg of stilbestrol did not appear to increase mortality from thromboembolic phenomena. It is to be emphasized that this type of prospective, well controlled study has not been performed in women receiving oral contraceptives.

Cerebrovascular Disease and Oral Contraceptives

We commented earlier on Inman and Vessey's[24] report of the association of cerebral thrombosis and embolism with oral contraceptive use. In

TABLE 12.—*Prostatic Cancer Patients Treated with 5 mg Stilbestrol Daily**

	Estrogen	*No Estrogen*
Total number patients	1,099	1,101
Deaths due to:		
Heart disease	146	103
Cerebrovascular accident	42	26
Pulmonary embolus	16	12

*Reprinted by permission from Bailar JC: Lancet 2:560, 1967.

TABLE 11.—*Death Rates per Million Women per Year Associated with Pregnancy, Contraceptives, and Certain Other Causes*§*

	Pregnancies		*Deaths Cause*	
Agent	*Number*	*Total*	*Pregnancy Itself*	*Contraceptive*
No contraceptive	800,000	200-1,000*	200-1,000	..
Rhythm method	230,000	60-300	60-300	None
Diaphragm	200,000	56-280	56-280	None
Condom	100,000	28-130	28-140	None
Intrauterine device	25,000	26-50	6-30	20†
Oral contraceptive	10,000	15-40	3-15	12-24‡

*Range of values from high to low socioeconomic status.
†FDA Advisory Committee on IUCD's, 1968, p. 7.
‡Based on USA and British estimates of risk, respectively.
§Reprinted by permission from Goldzieher JW: Contraception 1:409, 1970

1970, Masi and Dugdale[44] reviewed the English literature on this subject. Several individual or small numbers of case reports of cerebrovascular disease occurring in women taking oral contraceptives appeared in various American and British journals between 1962 and 1968. Walsh et al[45] reviewed the cases of 68 patients with neurological disease. Of these 68, four young patients on long treatment had pseudotumor cerebri, 17 had stroke, 20 had ocular involvement (optic neuritis or retinal vascular disease) and ten had migraine headaches. Obviously, this was not a controlled study but a review of neurologic disease in women receiving oral contraceptives. Other papers appeared, but again, controlled studies did not exist (for examples see Refs. 46-49). Finally, the study of Inman and Vessey[24] and Vessey and Doll[25] appeared which indicated an increased risk of cerebrovascular disease in women taking oral contraceptives. All cases of cerebral thrombosis were reviewed by a neurologist (without knowledge of the oral contraceptive use) and 19 were selected as meeting diagnostic criteria. Eleven (58 percent) had been taking oral contraceptives, whereas 18 percent would have been expected to have been taking them.

The study of Sartwell et al[27] also contained data on 13 patients with idiopathic intracranial vascular occlusion. Eight (62 percent) of the patients took oral contraceptives within one month of their illness; only 1 (8 percent) of the controls had done so. Most recently a collaborative study of stroke in young women was published.[50] For this study 12 neurologists reviewed cases of young women admitted to 91 participating hospitals in a two-year period. Five hundred ninety-eight nonpregnant women, aged 15 to 44 years, who had cerebrovascular disease, were reviewed. A detailed history of contraceptive use was obtained from 70 percent of the patients, and controls were obtained. The control group was selected from women with similar age, race and neighborhood of habitat. The findings which are summarized in Table 13 indicate a considerably greater use of oral contraceptives in the cerebrovascular patient group. The relative risk of cerebral vascular ischemia or thrombosis was estimated to be ninefold greater in women taking oral contraceptives than in those who do not.

In summary, data from well controlled studies of men receiving estrogens in high doses indicate that thromboembolic disease is increased. Similar well controlled studes have not been performed in women. Retrospective analysis of women having thromboembolic disease indicates that the percent taking oral contraceptives is greater than in a selected control group. In contrast, analysis of all the world literature, with summary of the incidence in all publications, fails to reveal an increased incidence of thromboembolism in women receiving oral contraceptives. Women antepartum, in whom high concentrations of estrogens and progestogens exist, do not appear to have increased likelihood of thromboembolic phenomena.

TABLE 14.—*Estimated Death Rate* from Several Causes in Women†*

	Age in Years	
	20-34	35-44
Pulmonary and central thrombo-embolism		
Nonusers of oral contraceptive	0.2	0.5
Users of oral contraceptive	1.5	3.9
Accidents	4.9	3.9
Cancer	13.7	70.1
Complications of pregnancy, delivery and puerperium	22.8	57.6

*Per 100,000 women per year.
†Modified from Inman and Vessey: Br Med J 2:193, 1968.

TABLE 13.—*Non-Matched Comparison of Use of Oral Contraception by Patients and Controls, According to Age†*

*Age Years**	*Cases of Stroke*			*Hospital Controls*			*Neighbor Controls*		
	Total Number	*Users*		*Total Number*	*Users*		*Total Number*	*Users*	
		Number	*Percent*		*Number*	*Percent*		*Number*	*Percent*
15-24	44	22	50.0	34	9	26.5	44	13	29.6
25-34	103	43	41.8	77	16	20.8	109	24	22.0
35-44	282	58	20.6	282	28	9.9	297	31	10.4
TOTALS	429	123	28.7	393	53	13.5	450	68	15.1

*Oral contraceptives used at reference date.
†Reprinted by permission from Collaborative Group Study of Stroke in Young Women. N Engl J Med 288: 871, 1973

It appears likely, based upon all these data, that very high doses of estrogens may increase the risk, but that lower doses may not. Since currently low-dose estrogen-progestogen combined contraceptives are commonly used, any risk that might exist with the high dose may be nonexistent or minimal with the low doses. Table 14 gives some relative incidence of mortality for oral contraceptives taking Inman and Vessey's data as a high estimate example, and comparing this with postpartum state, auto accidents and cancer to help put the figures in perspective. Progestogen-only oral contraceptives have not been implicated with increased risk of vascular disease.[39-43] Although the case for cause and effect of thromboembolic phenomena is on shaky ground, it would appear unwise to use estrogen containing oral contraceptives in women with clear-cut predisposing factors for thromboembolism. Such factors would include congestive heart failure, significant edema from any cause, obesity, varicose veins, and history of thrombophlebitis or embolism. The history and controversy of the relation of oral contraceptives to thromboembolism is an excellent example to point out the great need for carefully controlled clinical experimentation.

Effects of Oral Contraceptives on Carbohydrate Metabolism

GEORGE A. BRAY, MD*

THE INITIAL OBSERVATION of an impaired glucose tolerance in patients receiving oral contraceptives was made over ten years ago.[51] Since that time, this phenomenon has been examined in detail by many observers and has been reviewed several times,[52-54] most recently by Beck.[55] In the following discussion, we will examine this phenomenon in detail and attempt to answer three questions:

1. What are the impairments in glucose tolerance associated with ingestion of oral contraceptives?

2. Is the impairment of glucose tolerance the result of the estrogen, the progestogen or their combination?

3. By what mechanisms does this phenomenon occur?

The impairment of glucose tolerance is illustrated in Chart 10.[56] Two facts emerge: (1) The levels of fasting glucose are not significantly dif-

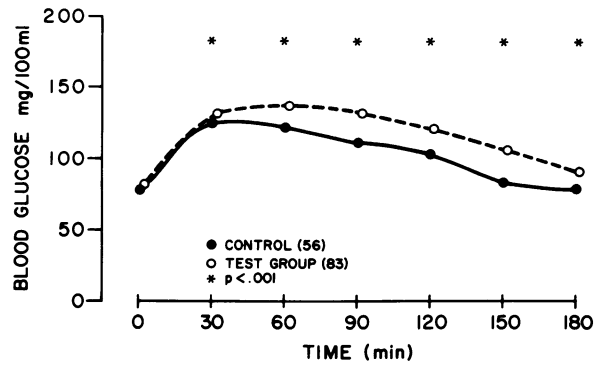

Chart 10.—Effect of oral contraceptives on glucose tolerance. This study adapted from Wynn and Doar[56] shows the impairment in glucose tolerance at all time intervals after the initial administration of glucose. Fasting levels of glucose, however, were normal. (Reproduced by permission from Wynn and Doar: Lancet 2: 715, 1966)

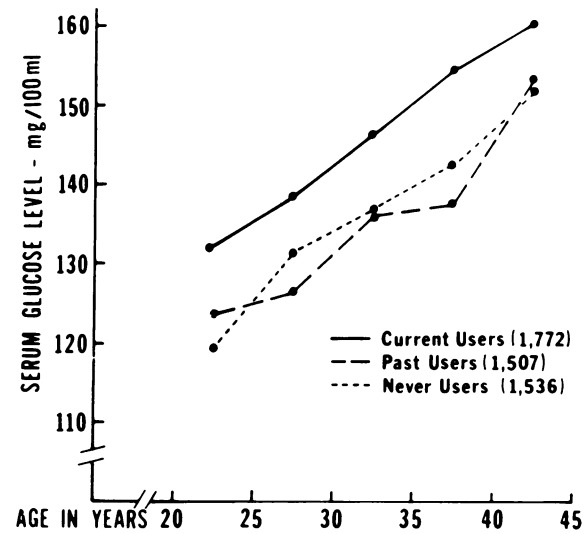

Chart 11.—Effect of age and oral contraceptives on glucose tolerance. The mean one-hour serum glucose concentrations after oral glucose, in current users, past users and non users of contraceptives steroids, is plotted against age. There was an increase in the levels of one-hour glucose value as a function of age. Women taking oral contraceptives had one-hour glucose values approximately 10 mg per 100 ml higher than the women who were not taking contraceptives or women who had previously taken them but had discontinued their use. (Reproduced by permission from Beck et al: Metabolism 22:846, 1973)

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